MODELLING AND ANALYSIS OF MUCUS TRANSPORT IN DISEASED AIRWAYS: EFFECTS OF CONSTRICTION OF AIRWAY DIAMETER

A Synopsis
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1 INTRODUCTION

The human body is a most important biomechanical system and the lungs are most amazing feats of nature. They pump vital oxygen through airways and into the bloodstream every time of every day. This pumping style is called human respiratory system. The respiratory system divided into two parts: upper airways and lower airway. The upper airways consists Nose, Para-nasal sinuses and Pharynx and lower airway system consists of the Begins with true vocal cords and extends to alveoli, Larynx, Trachea, Main stem bronchi, Segmental bronchi, Sub-segmental bronchi, Bronchioles, Terminal bronchioles, Respiratory bronchioles, Alveolar ducts, Alveolar sacs, alveoli and all the airways that complex branching of tube. The human gas exchanging organ, the lung, is located in the thorax (or chest). In the human lungs lined with a serous membrane, so called because it is exudes a thin fluid or serum, during the respiratory movements of the lung being eliminated by the lubricating actions of the serous fluid. They are lined by the typical respiratory epithelium with ciliated cells and numerous interspersed mucus-secreting goblet cells produce mucus while serous cells produce serous fluid, water like substance. The serous fluid behaves like a Newtonian fluid. Its viscosity varies from 0.01poise to 0.1poise. A mixture of lipoproteins called surfactant is secreted by special surfactant cells that are part of the alveolar epithelium and bronchioles, useful in mucus transport by causing slip at the inner wall of each lung. For further details, see Sleigh et al. (1988).

1.1 LUNG & RESPIRATORY SYSTEM

The lungs are essential organs of respiration, and gaseous-exchange between outside environment and blood is the main function. In the lung, Inhaled air passes along a branching network of airways which get deliberately narrower and shorter, terminating in small air sacs called alveoli. The largest airway is called the trachea (radius $\approx$ 0.9cm), designated as generation 0. The trachea is a tube formed of cartilage and fibro-muscular membrane, lined internally mucosa, Guyton (1991). The first generation of bronchus subdivided into secondary bronchi,

second generation bronchus also subdivided into tertiary and, the tertiary bronchi further subdivided into several generations of as numerously smaller bronchioles. It bifurcates down to roughly generation 23. The only 16 generations are conducting airways; to transport air from outside to gas exchange region is the main function. Generations 17 to 23 are called the respiratory airways. The alveolar sacs (radius 0.15mm), are found 17 generations onwards where gas exchange takes place, Hlastala (1996). Weibel (1963) has observed 23 generation of conducting airways trachea to terminal bronchiales in human respiratory system. Figure 1 shows the Weibel observation of the airway branching.

All lung airways are lined with a layer of fluid. The conducting airways are lined two-phases. At the base of the fluid lining are predominantly epithelial cells, the outermost cells of the airway wall. Above these cells there is an aqueous layer, known as the 'sol' phase, which surrounds epithelial cilia. Above the 'sol' phase is the 'gel' phase, a layer of mucus (Figure 2).

The mucus is secreted partly by individual goblet cells in the epithelial lining of the passage and partly by small sub-mucosal gland, Guyton (1991). The tips of the cilia penetrate the mucus blanket as they beat in a coordinated pattern [Schurch et al. (1999) and Gehr et al. (1993) (Figure 2)]. At total lung capacity, alveolar surface tension is approximately 30 dyn/cm but this reduces to <1 dyn/cm on expiration. The surface tensions of mucus and water are 40-50 dyn/cm and 70 dyn/cm respectively [Gehr et al (1990), (1996)].

	Generation		Diameter, cm	Length, cm	Number	Total cross-sectional area, cm^2
conducting zone	trachea	0	1.80	12.0	1	2.54
	bronchi	1	1.22	4.8	2	2.33
		2	0.83	1.9	4	2.13
		3	0.56	0.8	8	2.00
	bronchioles	4	0.45	1.3	16	2.48
	terminal bronchioles	5 ↓ 16	0.35 ↓ 0.06	1.07 ↓ 0.17	32 ↓ 6×10^4	3.11 ↓ 180.0
transitional and respiratory zones	respiratory bronchioles	17 18 19	↓ 0.05	↓ 0.10	↓ 5×10^5	↓ 10^3
	alveolar ducts	T_3 20 T_2 21 T_1 22	↓	↓	↓	↓
	alveolar sacs	T 23	0.04	0.05	8×10^6	10^4

Figure 1: Weibel's model of branching airways

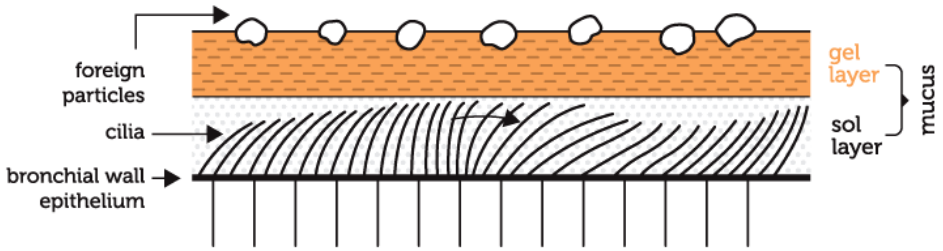

Figure 2: Airway Fluid Lining

1.2 CILIA

The cilia are microscopic, contractile filaments which act as sensory organs and perform many mechanical functions of the cell. The size, structure the pattern of motion of cilium. They are grown on ciliated cells of the epithelium at the rate of 200 cilia per cell i.e. 1500-2000 million cilia/cm^2. The length of cilia is 6-8 µm in man. The diameter of cilium is about 0.16-0.20 µm. Through their rapid 'beating' at 10–20 Hz and the resulting fluid flow generation, they perform a variety of functions, including the clearance of the protective airway surface liquid and reproductive tract. For cilia-driven flow, see Smith et al. (2008) and Sleigh et al. (1988) for the airway surface liquid. Internal cilia, however, typically interact with liquids such as mucus which have non-Newtonian properties such as viscoelasticity.

1.2.1 CILIA BEATING

In the respiratory tract, cilia beat in a continuous coordinated manner; generate a metachronal wave [Agrawal and Anawaruddin (1984)], moving the overlying mucus towards the pharynx. The rate of ciliary beat varies and it is approximately 20 beats/second. The pattern of ciliary beat consists of two parts, the effective stroke and the recovery stroke. During an effective stroke the cilium remains fully extended and moves through an arc in a plane approximately perpendicular to the cell surface. In the recovery stroke, a bend is propagated along the length of the cilium from base to tip, and the cilium swings around near the cell surface to reach the starting position for the next effective stroke [Sleigh (1991), see Figure 3 Ross & Corrsin(1974)]. The cilia tip velocity is 0.03 cm/sec. and the force exerted by single cilium is $4x10^{-7}$ dyne [Silberberg (1983)]. By combining many cilia together the stiffness of the organelles can be increased and much higher tip speeds than a single cilium. The rates of beating as well as cilia tip velocity are strongly influenced by viscosity of serous fluid in which they beat.

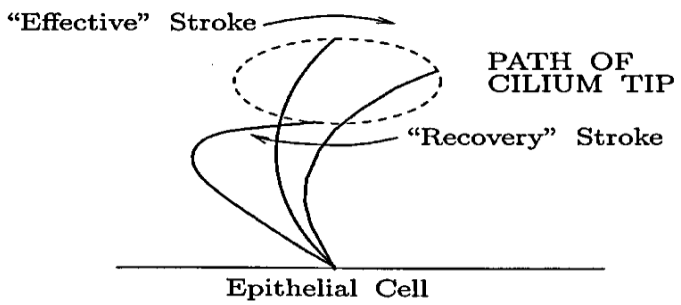

Figure 3: Idealised sketch of a cilium beat [Ross & Corrsin (1974)].

1.3 MUCUS AND MUCOCILIARY TRANSPORT

In airway the mucus layer works as liquid lining is to prevent dehydration of the epithelial cells and to protect the airways from external toxins by trapping inhaled particles in the mucus [Yeates (1991) and Grotberg (1994)] showing in Figure 2. The airway mucus is composed of mainly long chain glycoprotein and salts in a suspension of water, [Silberberg (1983), Sleigh (1981)]. The mucus viscosity may range from 10 poise to 103 poise at low shear rate (1 sec^{-1}) and it's magnitude is about 0.01 poise at high shear rate (100sec^{-1}),[Zahm et al. (1991), King (1980), Puchelle et al. (1983), King et al. (1993)].

Mainly it is an aqueous solution of mucin, which is shows elastic as well as viscous property but it does not behave as a simple viscous Newtonian fluid. It behaves like a non - Newtonian fluid, with relatively large relaxation times in comparison to the beat frequency of cilia. Mucus is transported from the smaller peripheral airways into the larger airways because of volume of mucus presents continues sheet, Sleigh et al. (1988). In the larger airways, in the absence of disease, the mucus layer has been found to be 5-10μm thick [Grotberg (1994) and Sleigh (1991)]. The mucus sheet can be described as a non-Newtonian, viscoelastic gel as it has both viscosity and elasticity. Initially the 'gel' will respond as a solid to the applied stress,

followed by a viscoelastic deformation and then a steady flow resulting in permanent deformation, King (2000).

The mucus transport towards the pharynx, together with any trapped particle is to be ciliary's propulsion (Figure 2). A reduction in periciliary fluid makes cilia beating more difficult and depletes the lubricant function, and both these effects inhibit mucociliary transport, Knowles and Boucher (2002). The mucociliary transport, the effect of the ciliary's action and flow of mucus from bronchioles, through the bronchi and trachea to the larynx, by which particulate matter is removed from the respiratory tract, which is cilia act in the periciliary (serous) fluid, a layer of low viscosity fluid underlying the mucus layer. The periciliary layer acts as a lubricant allowing mucus transport and preventing dehydration in the absence of mucus [Sleigh (1991), Knowles and Boucher (2002)]. The rate of transport increases from the smaller airways to the larynx. As the viscosity of the mucus increases, or the elasticity decreases, the transport rate is reduced King (2000).

1.4 THE FORCED EXPIRATION OR COUGH

It is a physiological mechanism, occurring in (homogenous) healthy lung, as well as in pathological subjects, with increasing mucus mass or when large particles enter the airways, the ciliary transport becomes inefficient and a more powerful mechanism is necessary, namely coughing [Lyubimov and Skobeleve(2000)]. Cough initiates when excessive amounts of any foreign matter or irritation exist in the bronchi and the trachea. The impulse to cough originates in the respiratory passages and automatic sequence events of follows. The human lung under pathological conditions is affected by various diseases such as, chronic bronchitis, Cystic fibrosis, Bronchial asthma, Lung cancer, Ciliary dyskinesia, etc. In the case of dyskinesia, cilia become immotile and in the case of cancer, loss of cilia mass may occur. Diseases in lungs are caused by

either removal of cilia or serous fluid. The cough reflex is associated with Asthama, Chronic bronchitis, [Mall (2008) and Guyton (1991)] etc.

The human cough has mainly two functions:

1. It helps to protect the lungs against expiration, and
2. It helps to propel secretions and other material upward through the airways.

During coughing, the pressure in the lung rises to as high as 100mm Hg or more, and the air is expelled at extremely high velocity approaching the speed of sound, Guyton (1991), and An inspiration of perhaps 2-2.5 liters of air.

1.5 MECHANISM OF MUCUS TRANSPORT DUE TO CILIA BEATING IN A NORMAL LUNG

Under normal conditions, cilia, serous fluid and mucus form the primary defence system of the lung for cleaning the inspired air contaminants, entrapped particles and cellular debris (Figure 2). The removal of these matters is affected by mucus transport caused by the cilia beating in the serous sub layer and by air motion during expiration [Sleigh et al. (1988)]. To understand this mechanism, there have been several experimental investigations related to rheological properties of mucus as well as about factors causing mucus transport due to cilia beating, [King et al. (1974), Chen and Dulfano (1976), King and Macklem (1977), King (1980), Winet and Blake (1980), Puchelle et al.(1983), Winet (1987)]. The sputum viscosity or visco-elasticity is above or below this range, the transport velocity decreases. King et al. (1974), while studying transport of various non-mucinous materials on mucus depleted frog palate found that their transport is severely decreased if the concentration of micro molecules in such material is either very high or very low. King (1980) in his experimental studies on frog palate has further pointed out that transport of canine tracheal mucus increases as elastic modulus increases. Winet and Blake (1980) studied the mechanics of mucociliary flows between two strips of frog palate epithelium forming a channel, the flow being caused due to static pressure drop across the

channel end and the resultant of the cilia tip velocities between two strips. Winet (1987) has also studied the role of periciliary fluid in mucociliary flows by observing velocity profiles over frog palate and pointed out that due to cilia beating mucus masses can be transported well behind the ciliary tips obviating the need for cilia tip penetration into the mucus. Puchelle et al. (1983) have conducted experiments in frog palates with both normal and pathological bronchial mucus. Current understanding is that the lining is a two-fluid model in which the upper layer is a viscoelastic gel (mucus, cross-linked glycoproteins) that overlies a sol layer (serous) Figure 2 [Foster (2002)].

It may be pointed out here that only a few analytical investigations have been conducted so far to develop a model for mucociliary transport in the respiratory tract [Barton and Raynor (1967), Blake (1975), Ross and Corrsin (1974), Winet and Blake (1980)]. Barton and Raynor (1967) have proposed a model for mucociliary transport under the assumption of a uniform mucus blanket supported on an oscillating piker force of cilia which wafts it towards and up the trachea but they did not consider the effect of periciliary fluid on the transport. Barton and Raynor (1967) have presented an analytical study of mucus transport caused by cilia motion by assuming cilium as a cylinder performing oscillating motion with greater height during effective strokes and lesser height during recovery strokes. The importance of airflow on mucus transport was investigated by Blake (1975) by considering two layer steady state Newtonian fluid models. Winet and Blake (1980) have also studied the mucociliary transport by using two layer Newtonian fluid models with differing viscosities; furthermore mucus transport rate is enhanced if the cilia just penetrate the upper more viscous mucus layer; however, as pointed out earlier, Winet (1987) also shown experimentally. King et al. (1993) have also proposed a planar non-symmetrical two layer fluid laminar flow model to study mucus transport in the respiratory tract due to cilia beating and air motion by considering mucus as a visco-elastic, its thickness, pressure drop, air stress and serous layer viscosity, etc. on mucus transport have been studied. It may be

noted here that the thickness of the serous layer has been assumed to be constant during beating in the study of King, et al. (1993). The pressure generation in the serous fluid which is supports the load of overlying mucus during cilia beating.

1.6 MECHANISM OF MUCUS TRANSPORT DUE TO COUGH IN A DISEASED LUNG

It is known that under pathological conditions of the lung, caused by diseases such as chronic bronchitis, cystic fibrosis, etc. excessive mucus is formed and it is transported by forced expiration or cough [King et al. (1985), King (1987), Sleigh et al. (1988)]. Also when airways are affected by immotile cilia syndrome (dyskinesia), cough is the main mechanism by which mucus is transported. In recent decades, several investigations, related to two phase flow in tubes under externally applied pressure have been conducted to simulate mucus transport in airways due to cough [Clarke and co-investigators (1970), Scherer and Burtz (1978), Scherer (1981), Kim et al. (1986)]. In particular, Clarke et al. (1970) have shown that the resistance to air flow through a liquid lined tube is markedly increased at all flow rates in comparison to the case of a dry tube. They have noted that at flow rates compatible with laminar flow conditions the pressure flow relationship in liquid lined tube is nonlinear and the resistance to the flow being greater than that expected from narrowing alone and have pointed out further that after the onset of turbulence there is a considerable increase in flow resistance which occur simultaneously with wave formation on the surface of liquid film. These effects are more marked in case of thicker liquid layer and with lower viscosity; effect of gravity is negligible on the mucus transport. Scherer and Burtz (1978), Scherer (1981) have conducted fluid mechanical experiments relevant to cough, using air and liquid blown out of a straight tube by turbulent air jet, they have shown that the liquid transport efficiency has positive correlation with the parameter ρ_a UT/μ (where ρ_a is the density of air, μ is the viscosity of liquid, U is the air velocity, T is the cough duration) and the

liquid transport decreases as this parameter decreases. They have further pointed out that for fixed. Values of ρ_a, U, T transport efficiency decreases as viscosity μ increases.

Several other investigations in a cough machine (a parallel plate channel) under turbulent flow condition have also been conducted by simulating mucus transport in the trachea due to cough [King et al. (1985, 1989), King (1987b), Zahm et al. (1991), Agarwal et al. (1989)]. In particular, Zahm et al. (1991) have also studied the effect of repetitive coughing on mucus transport in a simulated cough machine and noted a considerable decrease in mucus viscosity due to high shear rate during cough. Agarwal et al. (1994) studied, experimentally, the transport of mucus gel in a simulated cough machine where the bottom plate was grooved and flooded with serous fluid. They found that mucus transport increases as the cross-sectional area formed by grooves saturated with serous fluid increases, suggesting the importance of topography and slipperiness of the bottom surface. [M. Agarwal et al (1989)], and give the computer modeling that application to mucus transport in a cough mechanics simulating trachea [Satpathi et al. (2003)].

1.7 AIRWAYS RESISTANCE

During inspiration and expiration of airflow in the respiratory tract this concept is Airway resistance. The airflows through the trachea are not very massive or very viscous, but it is a noticeable hydraulic resistance, with the flow and a pressure drop along the airway. This pressure decreases in the direction of flow along airways. This pressure drop is also dependent on the flow rate in the airway, the viscosity of the fluid, and the pattern of flow. In the airways the airflow exists in three types Laminar, Turbulent, and Transitional. There is no flow along a airways unless there is a pressure difference, or pressure gradient, along the airway. When air flows at low rates in relatively small diameter tubes, as in the terminal bronchioles, the flow is laminar. Turbulent flow is a random mixing flow. When air flows at higher rates in larger diameter tubes,

like the trachea, the flow is often turbulent or truly turbulent, some of the flow in intermediate sized airways will be transitional flow in which it is difficult to predict if the flow will be laminar or turbulent. By Bio-fluid dynamics it is assumed the patterns in conducting zone i.e. turbulent airflow in bronchial generation I = 0-3 (inclusive of the trachea and main, lobar, and segmental bronchi); and laminar flow with a plug velocity profile in generation I = 4-16 (inclusive of the sub-segmental bronchi to terminal bronchioles) also the transitional and respiratory zone of generation II = 17-23. At breathing conditions the length-to-diameter ratios of the airways are too small for flows to become fully developed, Weibel(1963).

2 RESPIRATORY DISEASES

The lung disease means affecting the normal breathing functions causing temporary or permanent impairment of the lung function. These diseases can affect the whole or a part of the lung that includes the upper respiratory tract and lower respiratory tract. These diseases can be described many ways i.e. obstructive diseases, restrictive diseases, respiratory tract infections, tumors, pleural cavity diseases, pulmonary vascular diseases, disorders of airway breathing mechanics.

2.1 OBSTRUCTIVE LUNG DISEASES

Obstructive lung disease is a category of respiratory disease and it is characterized as airway obstruction. Obstructive lung disease narrowing the lumen area for airflow in smaller bronchi and larger bronchioles because of excessive contraction of the smooth muscle i.e. airway constriction, inflammation, collapsible airways, obstruction to airflow and problems to exhaling. Some examples are Asthma, Bronchiectasis, Bronchitis and Chronic obstructive pulmonary disease (COPD).

2.2 RESTRICTIVE LUNG DISEASES

Restrictive lung diseases are also known as interstitial lung diseases such as pleural or interstitial pulmonary diseases. It is restrict the lung expansion so decreasing the lung volume also the capacity.

3 AIRWAYS CONSTRICTION

The human respiratory system is generally circular, uniform, and smooth in shape as such air flows without any impedance to flow. When the diseased occur as asthma, COPD etc., the shape of respirator system inside or outside not always uniform they are constrircted, tapering inclining etc., due to non- uniformity arises a variation in pressure gradient of air flow. The effect of constriction on the lung is that a narrowing of the lumen of the bronchi, restricting airflow to and from the lungs. This is through the bronchoconstriction, is the constriction of the airways in the lungs due to the tightening of surrounding smooth muscle, with consequent coughing, wheezing, and shortness of breath. Bronchoconstriction can also be due to an accumulation of thick mucus. That causes of, the most common being emphysema, as well as asthma (Figure 4). Grainge et al. (2011) experimentally analysed that the compressive mechanical forces that arise during bronchoconstriction may induce remodeling independently of inflammation and concluded that bronchoconstriction without additional inflammation induces airway remodeling in patients with asthma.

Anafi et al.(2001) described the effect of bronchoconstriction on airway resistance is known to be spatially heterogeneous and dependent on tidal volume, the resistance, between flow and airway resistance mediated by parenchymal interdependence and the mechanics of activated smooth muscle for whole lung resistance and elastance. However, Olson et al. (2010) experimentally concluded that vital capacity is constricted lungs depend on the dynamic force length properties of smooth muscles that are the form of oscillatory force length behavior. Fahy

and Dickey (2010) explain structure and function of the normal airway, examine the normal formation of mucus (healthy state), clearance of airway mucus and dysfunction of mucus in diseases as constriction (Asthma, COPD, Cystic fibrosis).

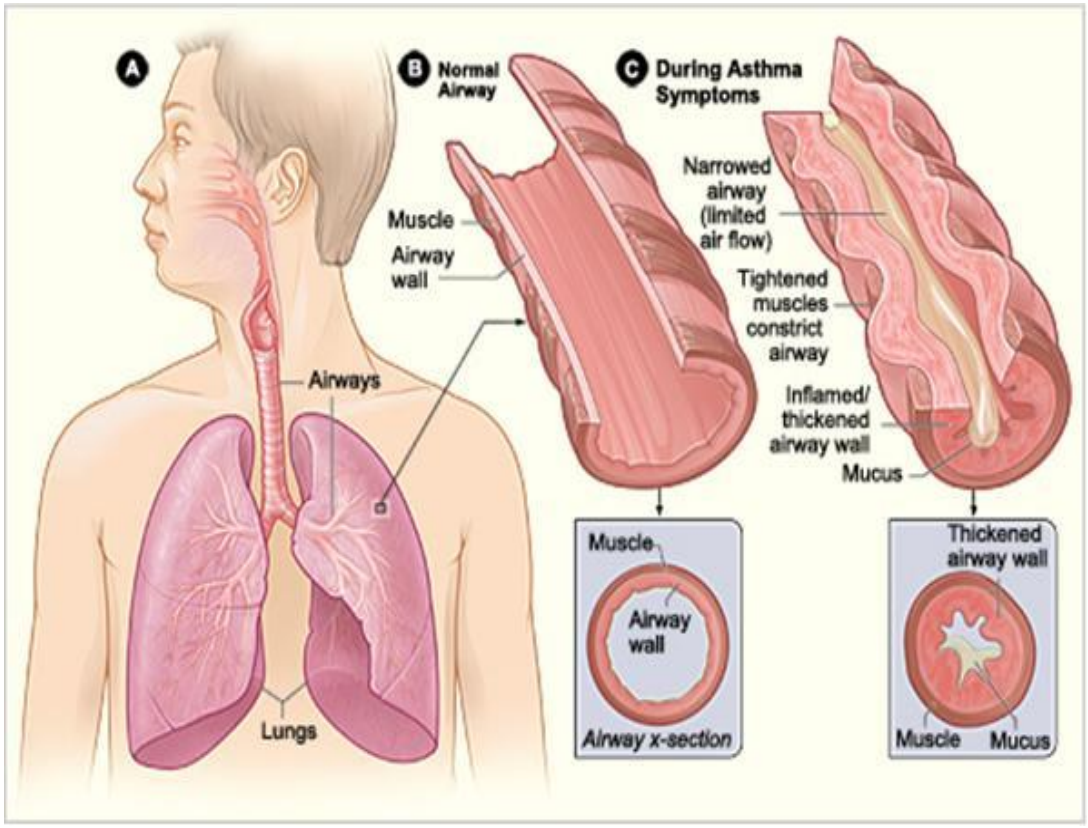

Figure 4: Asthma

4 SOME OTHER INTERESTING STUDIES

Saxena et al. (2015), (2010) investigate constant porosity of cilia bed and mucus viscosity, it is shown that air and mucus flow rates decrease with increase in serous fluid viscosity. The effect of porosity of cilia bed and cilia beating has been found to increase the air and mucus flow rates. Saxena et al. (2016) show the effects of serous fluid viscosity and porosity of cilia bed for mucus transport. Benjamin Mauroy et al. (2011) develop a model of mucus

clearance in idealized rigid human bronchial trees and focus our study on the interaction between (1) tree geometry, (2) mucus physical properties and (3) amplitude of flow rate in the tree. Tripathee , S. M., Verma, V. S. (2013) two layer steady state mathematical model and shown that mucus flow rate decreases as the viscosities of mucus and serous layer fluid increase and it increases as the air-velocity at the mucus-air interface, pressure drop and gravitational force increase. It has been also observed that mucus flow rate increases as the porosity parameter increase. Kumar et al.(2014), investigate mucus transport in constricted airway diameter decreases as diameter changes. Kumar et al.(2016) give a analytic and approximate result for the mucus transport in constricted airway decreases as diameter changes and shows that the air flow rate affected by mucus transport and mucus viscosity in the constricted airway. M. Chitra1 and S. Shabana (2017) shows the effects of slip parameter, viscosity on axial velocity profile, flow rate and wall shear stress of air region and mucus region for different constricted height and length of the human trachea are discussed graphically in constricted human airways. Norton et al (2011) observed that the transportability of mucus by cilial met is dependent on the rheological properties of the mucus because mucus is a non- Newtonian fluid that exhibits a plethora of phenomena such as stress relaxation, tensile stresses, shear thinning, and yielding the behaviour. Enault et al. (2010) gives a numerical investigation of basic interactions between respiratory mucus motion, air circulation and epithelium ciliated cells vibration. Smith et al. (2009), mathematical formulate cilia-driven flow occurs in the airway surface liquid model to the large-amplitude motion of a single cilium in a linear Maxwell liquid. Zahm et al.(2011), found that hyaluronan enhanced the transport of airway mucus by cilia and by cough: the lower the hyaluronan molecular weight, the higher the increase, also hyaluronan protects the airway epithelium against injury induced by bacterial products during infection. Low H.T. et al. (1997), considered the effect of non-Newtonian fluid viscosity by the power-law and Herschel-Buckley models of the speed of airway opening was determined under various opening pressure-velocity relationships, and based on an assumed shear rate gamma = U/ (0.5 H), where U and H are the

opening velocity and fluid film thickness, found that yield stress, like surface tension, increases the yield pressure and opening time. Shukla et al. (2016), and (2008) studied the effects of serous fluid viscosity, serous layer thickness, periciliary liquid viscosity, porosity of cilia bed, surfactant etc. on mucus transport in the human lung/smaller airways due to prolonged cough by taking two, three, and four layer models in which the central core air is assumed to flow under quasisteady state turbulent condition.

5 PROBLEMS TO BE STUDIED

It is noted here that in the above literature survey, the mucus transport in the normal lung by cilia beating and the mucus transport in the disease lung due to prolonged cough have been investigated.

The concept of constriction in mucus transport (Human Lungs) has not been taken up yet. So in our proposed work we will an attempt to study the effect of constriction on mucus transport in normal and diseased lungs by considering as planner model, circular model and multilayered model.

- Methodology

We have aimed to study the mucus transport by analytical approximate solution, governed by Navier-Stokes equations with initial, boundary and matching conditions for constricted airways (as Asthma etc.). MATLAB will be the instrument for computational work and graphical representation with relevant parameters (Weibel (1963), Kim (2015)).The aim of this proposed work is to deal with the role of mucus transport inside the constricted airways (diseased). The influence of several parameters, Newtonian and viscoelastic behavior of mucus, steady, unsteady, multi layered (Asthma, COPD, Cystic fibrosis etc.), nature in case of asymmetric constriction flow region, will be examined by using mathematical models in various cases:

(i) Mucus transport in the constricted lung due to prolonged cough: a three layer model with

effect of peripheral layer mucus viscosity and its thickness.

(ii) Mucus transport in the constricted lung due to prolonged or normal cough: a three layer model with effect of serous fluid viscosity and serous layer thickness.

(iii) Mucus transport in the constricted lung due to prolonged cough: a three layer model with effect of resistance to flow by serous fluid in the cilia bed.

(iv) Mucus transport in the constricted lung due to prolonged cough: a four layer model with effect of resistance to flow by serous fluid in the cilia bed.

(v) Mucus transport in the constricted lung due to prolonged cough: a three layer model with effect of periciliary liquid viscosity and porosity of cilia bed

(vi) Mucus transport in the constricted smaller airways due to prolonged cough: a three layer model with effects of surfactant on the wall.

(vii) Mucus transport in the smaller airways due to prolonged cough: a three layer model with effects tapered constriction and mucus viscosity

It is hoped that the study in the thesis would be helpful in curing persons suffering from asthma and other lung diseases. The proposed work will have its significance pertaining to lung related issues e.g. Asthma, bronchitis, cystic fibrosis etc.

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